3/3/04

REMARKS

The gracious telephonic discussion granted applicants' attorney is gratefully acknowledged.

The first rejection is concerned with lack of an adequate written description under 35 USC §112 ¶1. The Examiner states, "These arguments have been fully considered but found unpersuasive because the specification does not describe what constitutes a wild-type TSG 101 protein with any associated function."

The first issue raised is whether the two species are sufficient to support the genus of claim 23. Of course, this rejection is not pertinent to claim 25 and it is believed that this claim should not have been included in this rejection. However in contradistinction to the Examiner's statement, on page 4 of the application, lines 18-21, it is stated, "The *TSG101* genes and fragments thereof, encoded protein, and anti-TSG101 antibodies are useful in the identification of individuals predisposed to development of such cancers, and in characterizing the phenotype of sporadic tumors that are associated with the gene." On page 15, lines 14-16, it is stated, "The structure of TSG101 indicates that it is a transcription factor, which may act as a downstream effector of stathmin signaling."

The conservation of sequence of the mouse and human TSG101 proteins is commented upon on page 38, lines 11 – 26, where it is stated, "The extraordinary conservation observed between the mouse and human TSG101 proteins is consistent with its important biological role. Both the coiled-coil and proline-rich domains are nearly identical, and the potential phosphorylation and N-glycosylation sites are completely conserved between the human and mouse protein."

Therefore, the subject application does teach that one would expect that the family of TSG101 proteins of different species would have great similarity. Not only are the sequences conserved, but important domains are also conserved. In the absence of any evidence to the contrary, the bald statement that there is insufficient evidence to support claiming the mammalian genus is unsubstantiated and is contrary to the available evidence. This rejection should be withdrawn in the absence of evidence that one would expect substantial deviations from the sequences described in the subject application.

The rejection goes on to say, "The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof."

On page 15, line 26 to page 16, line 22, the preparation of antibodies is discussed. Further it is stated on page 16, line 23 to page 19, line 27, the use of the antibodies is described. Particularly, the antibodies find use in diagnostic assays for staging, detection and typing of tumors (page 16, lines 24-25); "a reduction in normal TSG101 and/or presence of abnormal TSG101 is indicative that the tumor is TSG101 associated. (page 16, lines 27-28); and detection of metastasis (page 17, lines 8-9). Various methods of

performing immunoassays with the antibodies are described throughout the portion indicated above.

The relationship between cancer and abnormal TSG 101 is described on page 37, lines 9 to page 38, line 10.

There can be no question that from having the protein and the directions in the application, antibodies to the protein, both polyclonal and monoclonal, can be prepared. The preparation of antibodies is so well established that the courts accept the fact that having the protein is tantamount to being able to produce antibodies specific for the protein. In fact, antibodies are defined by the protein to which the antibody binds, rarely, if at all, is the sequence of the antibody determined. The function of the TSG101 protein is amply defined and the use of the antibodies in diagnostic assays associated with the detection of TSG101 is amply described. The sequence of the mouse and human proteins is set forth, so that anyone can reproduce the proteins. Various conformational and structural aspects of the proteins are described and their similarity remarked upon. It is submitted that the requirements set forth in the Final Rejection are all present in the subject application. It should follow that this rejection should be withdrawn.

In Noelle v. Lederman, 02-1187, CAFC, 2004, the Court had occasion to consider what was required for a written description of an antibody. The Court stated,

"The court adopted the USPTO Guidelines as persuasive authority for the proposition that a claim directed to "any antibody which is capable of binding to antigen X" would have sufficient support in a written description that disclosed "fully characterized antigens." Synopsis of Application of Written Description Guidelines, at 60, available at http://www.uspto.gov/web/menu/written.pdf (last visited Jan. 16, 2003) (emphasis added).

Therefore, based on our past precedent, as long as an applicant has disclosed a "fully characterized antigen," either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that described antigen."

The Court went on to say:

"Noelle did not provide sufficient support for the claims to the human CD40CR antibody in his '480 application because Noelle failed to disclose the structural elements of human CD40CR antibody or antigen in his earlier '799 application. Noelle argues that because antibodies are defined by their binding affinity to antigens, not their physical structure, he sufficiently described human CD40CR antibody by stating that it binds to human CD40CR antigen. Noelle cites Enzo Biochem II for this proposition. This argument fails, however, because Noelle did not sufficiently describe the human CD40CR antigen at the time of the filing of the '799 patent application. In fact, Noelle only described the mouse antigen when he claimed the mouse, human, and genus forms of CD40CR antibodies by citing to the ATCC number of the hybridoma secreting the mouse CD40CR antibody. If

Noelle had sufficiently described the human form of CD40CR antigen, he could have claimed its antibody by simply stating its binding affinity for the "fully characterized" antigen. Noelle did not describe human CD40CR antigen. Therefore, Noelle attempted to define an unknown by its binding affinity to another unknown. As a result, Noelle's claims to human forms of CD40CR antibody found in his '480 application cannot gain the benefit of the earlier filing date of his '799 patent application." (emphasis added)

Please note that the bold statement states that if Noelle had sufficiently described the human form of the CD40R antigen, he could have claimed the antibody to the antigen. Applicants fulfill this requirement in providing the complete sequence of the human, as well as the mouse protein. Applicants further provide a utility for both the protein and antibodies to the protein. In considering the Noelle disclosure, the Court specifically relied on the standards set forth in *Vas-Cath Inc. v. Mahurkar,* the same case relied upon by the Examiner. Based on the Court's clear statement of what is required for a claim to an antibody, the Examiner is respectfully requested to withdraw this rejection.

The next rejection is under 35 USC §103 based on Macuer. Macuer teaches that he isolated a nucleic acid sequence that is a fragment of the TSG101 sequence taught by applicants. At no time does Macuer suggest that he used the defined sequence to express the polypeptide for which the sequence encodes. Nor does Macuer suggest that the sequence begins with a particular codon, so that Macuer would have had to prepare three sequences to ensure that the sequence was in frame and then would have had to determine which of the three polypeptides the right polypeptide was. It is not clear from Macuer that Macuer could be certain that his sequence had the right reading frame. Therefore, Macuer did not have the polypeptide of the subject protein, until it was established that he had the correct reading frame. This could only be assured when one had the entire sequence, had expressed the gene and shown that the natural protein and the recombinant protein were the same.

There is the further consideration that Macuer never had the polypeptide. The Examiner is therefore building conjecture on conjecture. There can be no certainty that a fragment of a protein will provide an antibody that will have specific affinity to the antigen. This is particularly true for monoclonal antibodies that do not have the high affinity of a polyclonal antibody composition. Whether one could prepare a monoclonal antibody that had useful specificity for the antigen is entirely conjectural until one performs the necessary investigation. That one could perform the necessary investigation is not a substitute for having performed such investigation. Until the experiment is performed and the necessary controls performed, it is entirely speculative that Macuer had anything other than a fragment of a gene that is related to the sequence taught by applicants. Therefore, claim 24 has an independent basis for patentability, since the monoclonal antibody requires even greater conjecture than antibodies generically.

Patents not only encourage invention and disclosure, they encourage investment in the development of a product. As such, the public has required that the inventor

establish that the inventor has "possession" of the invention at the time of filing. While it is well established that a reference does not need to have the same level of enablement as a patent application, nevertheless the reference should have a reasonable teaching with a reasonable degree of definiteness. The reference should not be speculative or conjectural, but rather should provide some assurance of success, should one follow its teaching. Macuer does not teach that one should produce antibodies, since Macuer did not have a polypeptide from which antibodies could be produced. Macuer does not teach that if one expressed his fragment, that the antibodies that are produced would bind to the natural protein. Applicants are not claiming antibodies that bind to the conjectured Macuer polypeptide, but to the wild-type antigen. One cannot say with any reasonable certainty that an antibody produced to the fragment would bind with sufficient specificity to the wild-type antigen. Rather, one must conjecture that the Macuer fragment, if expressed, would have a conformation that sufficiently approximated the antigen, so as to produce antibodies that would recognize the wild-type antigen.

The rejection states that it would have been obvious to make an antibody to the sequence from the Macuer sequence. As discussed above, this is not sufficient since there is no showing that such antibody would also bind the wild-type antigen, rather than the denatured antigen. Because the procedures are known, does not necessarily mean that the outcome is known. It is the Examiner's conjecture that one would have been sufficiently motivated to use the Macuer fragment to make an antibody. This is not found in the reference, but rather based on the Examiner's speculation. Inductive logic should not be the basis for a rejection. Rather, the Examiner should point to the place in the reference that the reference teaches that the fragment should or would be used to prepare an antibody.

Why not say that an HIV vaccine is obvious? The HIV antigens are known, the sites that bind to cellular proteins are known, and there is substantial information about the mechanism of entry and proliferation. What is there left to do to produce an effective vaccine? Yet, there is no vaccine and at the moment a highly criticized clinical study is being carried out using a combination of vaccines that individually have been found to be ineffective. If one were to find an effective HIV vaccine, the same logic that is used in rejecting the subject claims would find such vaccine obvious. It is submitted that a rejection should not rely on there being known procedures for performing a research project. Rather, a rejection should demonstrate that there was a clear interest to perform the procedures in the reference, that the procedures are well known and accepted as being routine, and that there is a high likelihood of success in obtaining the desired result. As amply shown, there was no reasonable expectation of success to produce antibodies that would usefully bind to the **wild-type** antigen. Producing antibodies is not the same as producing antibodies specific for a wild-type conformation.

In light of the above remarks, the Examiner is respectfully requested to withdraw the rejections and pass this application to issue. If the Examiner believes that a telephonic interview would expedite the prosecution of this application, she is respectfully requested to call the undersigned at 650 344 4674.